(a) a polynucleotide encoding the same polypeptide as encoded by the human cDNA in ATCC Deposit No. 75899; and

(b) the complement of (a).

33. The isolated polynucleotide of claim 32, wherein the member is (a).

34. The isolated polynucleotide of claim 32, wherein said polynucleotide comprises DNA identical to the coding portion of the human cDNA in ATCC Deposit No. 75899.

35. An isolated polynucleotide encoding a polypeptide comprising the amino acid sequence of SEQ ID NO:2, except for at least one conservative amino acid substitution.--

In the Figures:

Please replace Figures 1A and 1B with substitute Figures 1A and 1B, attached hereto.

Please replace Figure 2 with substitute Figure 2, attached hereto.

Remarks

The specification has been amended to include section headings, claim priority to the earlier filed PCT application, correct typographical errors, and insert SEQ ID NOS.

Further, a substitute sequence listing and substitute Figures 1 and 2 are submitted herewith to correct nucleotide and amino acid sequence errors (SEQ ID NOS: 1 and 2) in the original listing.[2] It is believed that these changes do not introduce new matter, because the

[2] The specific changes to the sequences were discussed with the Examiner by telephone on January 24, 1997, and are discussed in the text below.

correct sequences were inherent to the ATCC deposited clone, ATCC Deposit No. 75899, which was deposited prior to the filing of the present application.

Claims 8-20 have been canceled pursuant to a restriction requirement dated September 30, 1996. In addition, claims 1-7 have been canceled in favor of new claims 21-35, which find support in the claims as originally filed and throughout the specification. *See, e.g.*, page 6, lines 9-14; page 10, line 29, to page 11, line 3; page 11, last paragraph, to page 12, first paragraph; and page 12, line 26, to page 13, line 6. No new matter has been added.

Thus, claims 21-35 are pending in the application. Based on the above amendments and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Priority

At page 1, item 2, of Paper No. 12, the Examiner states that Applicants have not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 120. Applicants have amended the specification herein to refer to the priority PCT application, PCT/US95/03216. A Request for Corrected Official Filing Receipt is also being filed concurrently herewith to include the PCT priority information. This objection is now moot, and withdrawal thereof is respectfully requested.

Objections Concerning the Sequence Listing

At page 2, item 3, of Paper No. 12, the Examiner states that "Figure 3 discloses amino acid sequences for 'TNFR2 human' and 'consensus', which are not listed in the paper copy of the sequence listing."

At the outset, Applicants note that there was no Figure 3 filed with the application. Applicants assume, therefore, that the Examiner must have intended to object to original Figure 2, which contained amino acid sequences for "TNFR2 human" and the "consensus" sequence. As discussed above, however, substitute Figure 2 is being submitted herein to reflect the corrected amino acid sequence for the polypeptide of the invention. Accordingly, the "TNFR2 human" sequence (lower line of new Figure 2) has been included, as "SEQ ID NO:3," in the attached substitute sequence listing. Thus, the Examiner's objection regarding the TNFR2 human sequence has been accommodated. However, since there is no longer a consensus sequence in new Figure 2 (connecting lines, rather than specific sequences, indicate the "consensus"), no sequence listing is required. It is believed that this objection has been overcome, and withdrawal thereof is respectfully requested.

At pages 2-3, item 4, the Examiner objects to the specification (page 5, FIG. 1 legend and page 6, FIG. 2 legend) because it is missing reference to an appropriate SEQ ID NO, and therefore is not in compliance with 37 C.F.R. § 1.821(d). Applicants have amended the specification herein to insert the missing SEQ ID NOS requested by the Examiner. This objection has been overcome and withdrawal thereof is respectfully requested. Further in this regard, Applicants have adjusted some of the original SEQ ID NOS to reflect the addition of the TNFR2 human sequence as SEQ ID NO:3 *(i.e.,* original SEQ ID NO:3 is now SEQ ID NO:4, and so on).

In addition to correcting the sequence listing to add the Figure 2 TNFR2 human sequence as SEQ ID NO:3, SEQ ID NOS: 1 and 2 have been updated in the substitute sequence listing to reflect the correct nucleotide (SEQ ID NO:1) and amino acid sequence (SEQ ID NO:2). Substitute SEQ ID NO: 1 differs from the original SEQ ID NO:1 by: (1) including additional flanking regions (nucleotides 1-45 and 1217-1248); and (2) deleting one nucleotide ("C") at position 1076 of the original SEQ ID NO:1, resulting in a frameshift for the remainder of the sequence. Substitute SEQ ID NO: 2 differs from original SEQ ID NO:2 in that the amino acids at positions 338-380 of new SEQ ID NO:2 differ from the amino acids at position 338-369 of the original SEQ ID NO:2. This change in amino acids results from the frameshift in the nucleotide sequence described above. These amendments do not introduce new matter since the correct sequences (i.e., substitute SEQ ID NOS: 1 and 2) are inherent in and therefore supported by the deposited clone, ATCC Deposit No. 75899, which was deposited on September 28, 1994 (prior to the filing of the present application). *See*, the specification at page 6, lines 13-14.

Thus, in accordance with 37 C.F.R. § 1.825(a), the amendments included in the substitute sheets of the sequence listing are supported in the application, as filed, at page 6, lines 13-14 and therefore include no new matter. In accordance with 37 C.F.R. § 1.825(b), the substitute paper copy of the sequence listing and the substitute computer readable copy of the sequence listing submitted herewith are the same.

In addition, owing to the sequence corrections in SEQ ID NOS: 1 and 2, discussed above, Applicants also submit herewith substitute Figures 1 and 2. Substitute Figures 1 and 2 now reflect the correct nucleotide and amino acid sequences for the human TNF receptor of the invention. The corrected sequences are inherent in the deposited clone ATCC Deposit No. 75899, which was deposited on September 28, 1994 (prior to the filing of the present

application). *See*, the specification at page 6, lines 13-14. Thus, it is believed that no new matter has been added.

In addition, substitute Figure 1 differs from original Figure 1 in that a *21* amino acid leader sequence is underlined compared to an underlined *16* amino acid leader sequence, in original Figure 1. This change, however, does not introduce new matter because the original specification, at page 5, lines 29-30, states that "[t]he initial 21 amino acids [of Figure 1] represent the putative leader sequence and are underlined." Therefore, the underlined leader sequence in new Figure 1 now corresponds to the original specification.

Rejection under 35 U.S.C. § 112, first paragraph (scope)

At page 3, item 5, of Paper No. 12, the Examiner rejects claims 1-7 under 35 U.S.C. § 112, first paragraph, as the specification is allegedly enabling only "for the disclosed nucleic acids comprising the sequence encoding SEQ ID NO:2, the mouse homolog, and allelic variants." The Examiner contends that the specification does not reasonably provide the full scope of enablement for the whole genus of variants or fragments of polynucleotides encoding SEQ ID NO:2.

More specifically, the Examiner objects to the "at least 70% identical" language and the word "fragment" appearing in original claims 1 and 3, and "variants" and "fragment of SEQ ID NO:2" language in original claims 6 and 7. The Examiner's rationale for the rejection is set forth on pages 3-8 of Paper No. 12. In short, the Examiner's position is that the variants and fragments [of the originally claimed invention] encompass a genus with a large number of species which are not functional. The Examiner concludes that in view of the extent and the unpredictability

of the experimentation required to practice the invention as claimed, one skilled in the art could not make the invention without undue experimentation.

Applicants traverse this rejection as it may be applied to new claims 21-35. Applicants emphasize that the "capable of hybridizing", "70% identical", and "polynucleotide fragment" language has been deleted from the new claims. Thus, Applicants believe that these grounds for the rejection have been rendered moot.

Applicants request that the Examiner revisit the issue of enablement in light of new claims 21, 32, and 35. In short, claims 21 and 32 read on nucleic acid molecules at least 95% identical to those encoding the recited amino acid sequences. Applicants submit that the language "at least 95% identical" is enabled by the specification (*see, e.g.*, the specification at page 10, line 29, to page 11, line 3) and the state of the art at the time the present application was filed for the following two reasons. First, at the time of filing, only routine experimentation would have been required to generate or identify nucleic acid molecules at least 95% identical to those recited in the claims. Second, only routine experimentation would have been required to determine a use for such "at least 95 % identical" polynucleotides. These two reasons why the currently pending claims are enabled are discussed below in turn.

I. At the time of filing, routine methods were available for determining the percent identity between two nucleic acid sequences

As the Examiner is aware, computer algorithms were available to the skilled artisan for identifying nucleic acid sequences at least 95% identical to the sequences of the polynucleotides recited in the claims. For example, the well-known Bestfit program (Wisconsin Sequence Analysis Package, Version 8 for Unix, Genetics Computer Group, University Research Park, 575

Science Drive, Madison, WI 53711), which uses the local homology algorithm of Smith and Waterman (Advances in Applied Mathematics *2*: 482-489 (1981)), could have been used to generate a percent identity between two nucleotide sequences. Thus, it is beyond question that only routine experimentation would have been required to generate or identify polynucleotides having a nucleotide sequence at least 95% identical to the sequence of the polynucleotides recited in the claims.

II. At the time of filing, only routine experimentation would have been required to determine a use for such "at least 95% identical" polynucleotides

At the outset, Applicants would like to point out that the claims read on a polynucleotide at least 95% identical to one of those recited in the claims irrespective of whether the polynucleotide encodes a polypeptide having human TNF receptor activity. This is because even where a particular nucleic acid molecule does not encode a polypeptide having human TNF receptor activity, the skilled artisan would still know how to use the nucleic acid molecule, for instance, as a hybridization probe or as a polymerase chain reaction (PCR) primer. See, the specification at page 10, lines 24-28. As discussed in the specification, such uses include, *inter alia*, (1) isolating the human TNF receptor gene or an allelic variant thereof in a cDNA library; (2) *in situ* hybridization (e.g., "FISH") to metaphase chromosomal spreads to provide the chromosomal location of the human TNF receptor gene (*see*, for example, Verma *et al., Human Chromosomes: A Manual of Basic Techniques*, Pergamon Press, New York (1988); and (3) Northern blot analysis for detecting human TNF receptor gene expression in specific tissues.

Thus, from above, at the time of filing, it is clear that the skilled artisan would have known "how to use" polynucleotides at least 95% identical to those recited in the claims for at

least some practical diagnostic purpose. As the Examiner is aware, this is all that the law requires where the claims are directed to a polynucleotide *per se*. Accordingly, Applicants believe that new claims 21-35 satisfy the requirements of 35 U.S.C. § 112, first paragraph.

However, even assuming *arguendo* that the currently pending claims did require a polynucleotide that encodes a polypeptide having human TNF receptor activity, the claims would still be enabled for the following two reasons. First, at the time of filing, the skilled artisan was fully aware of amino acid changes that are either less likely or not likely to significantly affect protein function. Second, routine *in vitro* assays were known in the art for measuring human TNF receptor activity.

A. At the time of filing, the skilled artisan was fully aware of amino acid changes that are either less likely or not likely to significantly affect protein function

Guidance concerning how to make phenotypically silent amino acid substitutions is provided in Bowie *et al.*, "Deciphering the Message in Protein Sequences: Tolerance to Amino Acid Substitutions," *Science 247:*1306-1310 (1990), wherein the authors indicate that studies have revealed that proteins are surprisingly tolerant of amino acid substitutions. The authors further indicate which amino acid changes are likely to be permissive at a certain position of the protein. For example, most buried amino acid residues require nonpolar side chains, whereas few features of surface side chains are generally conserved. Further, the following conservative amino acid substitutions were well known in the art at the time of filing.

Aromatic	Phenylalanine Tryptophan Tyrosine
Hydrophobic	Leucine Isoleucine Valine
Polar	Glutamine Asparagine
Basic	Arginine Lysine Histidine
Acidic	Aspartic Acid Glutamic Acid
Small	Alanine Serine Threonine Methionine Glycine

Moreover, amino acids in the human TNF receptor polypeptide sequence of the invention that are essential for function could have been identified by methods known in the art, such as site-directed mutagenesis or alanine-scanning mutagenesis (Cunningham and Wells, *Science 244*:1081-1085 (1989)). The latter procedure introduces single alanine mutations at every residue in the molecule. The resulting mutant molecules are then tested for biological activity using an appropriate *in vitro* assay. Thus, at the time of filing, it was well within the realm of the skilled artisan, based on the general state of the art, to judiciously select amino acid substitutions or alterations that would have been *likely* to exhibit most, if not all, of the biological activity of the parent polypeptide, and *unlikely* to have a detrimental effect on human TNF receptor protein function.

B. At the time of filing, routine in vitro assays were known in the art for measuring human TNF receptor activity

At the time of filing, *in vitro* assays (*i.e.*, competitive binding assays) were available that would have allowed one skilled in the art to routinely screen candidate polypeptides to determine those that exhibit human TNF receptor activity (*i.e.*, the ability to bind human TNF). Due to the fact that the skilled artisan would have known how to make conservative amino acid changes, it would not have been an infrequent event to find such "at least 95% identical" polynucleotides that encode polypeptides exhibiting human TNF receptor activity. Again, this is all that the law requires for enablement.

In this regard, the Examiner is reminded of *Ex parte Mark*, 12 USPQ2d 1905 (BPAI), which stands for the proposition that claims directed to a "biologically active" protein are enabled if, at the time of filing, it would have been routine for the skilled artisan to identify such a protein using a conventional screening assay. Thus, the fact that any *given* candidate polypeptide might not have human TNF receptor activity does not militate against a conclusion of enablement provided that one skilled in the art could have readily assayed even a large number of candidates to find at least a reasonable number of "winners." Clearly, in the present situation, the skilled artisan could have generated at least a reasonable number of polypeptides having human TNF receptor activity that were encoded by a polynucleotide having at least 95% identity to those recited in the claims.

For all these reasons, it is respectfully submitted that the present enablement rejection under 35 U.S.C. § 112, first paragraph has been overcome, and is not applicable to new claims 21-35. Withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 112, first paragraph (deposit)

At page 8, item 6 of Paper No. 12, the Examiner rejects claim 3 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Specifically, the Examiner contends that:

> a deposit of the ATCC Deposit No. 75899 is required to enable the invention of claim 3. This determination has been made because the claimed ATCC Deposit No. 75899 properties have not been fully disclosed or the materials required to construct the claimed ATCC Deposit No. 75899 have not been shown to be publicly known and fully available. The specification does not teach how to make the ATCC Deposit No. 75899 on page 6 (second paragraph), pages 35 (last paragraph) through 38, and page 41 (first paragraph), in a sufficient manner to practice the invention because one skilled in the art could not determine the exact materials necessary to construct the ATCC Deposit No. 75899. It would require undue experimentation to determine the exact materials necessary to construct the ATCC Deposit No. 75899. Without a publicly available deposit of the above polynucleotide, one of ordinary skill in the art could not be assured of the ability to practice the invention as claimed. A suitable deposit for patent purposes is required. It should be noted that the specification (pages 10-11) does not state that the material was deposited under the terms of the Budapest Treaty.

Paper No. 12 at page 9.

Solely to expedite prosecution, Applicants submit herein an executed Declaration of Deposit, indicating the terms of the deposit of ATCC Deposit No. 75899. Further, the specification has been amended at page 6 to insert the address for the ATCC depository (*See*, 37 C.F.R. § 1.809(d)(4)). This rejection is now moot, and withdrawal thereof is respectfully requested.

B

Rejections under 35 U.S.C. § 102

At page 11, item 8, of Paper No. 12, the Examiner rejects claims 1-7 under 35 U.S.C. § 102(b) as being anticipated by Lewis *et al.* (1991). Applicants traverse this rejection as it may be applied to new claims 21-35.

It is the Examiner's position that Lewis *et al.* disclose the cloning of the mouse TNF receptor cDNA and the deduced amino acid sequence. In summary, the Examiner concludes that the Lewis *et al.* teaching meets the "70% identical to the polynucleotide encoding SEQ ID NO:2" language in original claims 1 and 3. Applicants submit that the new claims 21-35 do not contain this language and therefore are not anticipated by Lewis *et al.* Therefore, this rejection should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete response has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned directly at (202) 371-2637.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

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